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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/601,140	KAUPPINEN ET AL.	
	Examiner	Art Unit	
	Robert T. Crow	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-140* is/are pending in the application.

4a) Of the above claim(s) *23,24,81-89,94-109 and 120-126* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22,25-80,90-93,110-119 and 127-140* is/are rejected.

7)☒ Claim(s) *9,17,55,92 and 138* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *20 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I and species SEQ ID NO: 3 in the reply filed on 21 April 2006 is acknowledged. The traversal is on the ground(s) that the search would not be burdensome. These arguments are not found persuasive because, as stated on page 5 of the Requirement for Restriction/Election, the inventions have acquired a separate status in the art because of their recognized divergent subject matter as exemplified by their different classification. Furthermore, a search for the inventions of all of the groups would not be co-extensive because a search indicating the ***process is*** novel or nonobvious would not extend to a holding that the ***product itself is*** novel or nonobvious; similarly, a search indicating that ***the product is*** known or would have been obvious would not extend to a holding that ***the process is*** known or would have been obvious.

The requirement is still deemed proper and is therefore made FINAL.

Claims 81-89, 94-109, and 120-126 are therefore withdrawn. Claims 23-24 are withdrawn, as claim 23 is drawn to a non-elected sequence. Claims 25 and 26 are interpreted as being drawn the elected sequence SEQ ID NO. 3 (i.e., compound 3).

Claims 1-22, 25-80, 90-93, 110-119, and 127-140 are currently under prosecution.

Claim Objections

1. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 87-135 been renumbered 92-140 and have been corrected for dependency. In addition, renumbered claim 93 is interpreted as being dependent on renumbered claim 92.

2. Claims 9, 17, 55, 92, and 138 are objected to because of the following informalities:

A. The amendment to claim 9, i.e., "[capture probe/," begins with a bracket but does not end with a bracket. Appropriate correction is required.

B. The amendment to claim 17, i.e., "[probe/," begins with a bracket but does not end with a bracket. Appropriate correction is required.

C. Claim 55 recites "the said LNA" in line 3 of the claim. This redundancy appears to be a typographical error. Appropriate correction is required.

D. Claim 92 recites "a target nucleic acid molecule the nucleotide sequence which" in lines 1-2 of the claim. This appears to be a typographical error. Appropriate correction is required.

3. Claim 138 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 137. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-15, 22, 27-29, 33-34, 37-38, 42-43, 45-47, 58, 59, 113, and 117 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 9 is indefinite in the recitation "a homopolymeric nucleotide" in line 2 of the claim. It is unclear how a nucleotide, which comprises a single base, is polymeric.

2. Claims 9-15, 27-29, 33-34, and 45-47 are indefinite in the recitation "at least about " in lines 2-3 of claim 9 and in line 2 of each of claims 10-15, 27-29, 33-34, and 45-47. The phrase "at least" typically indicates a minimum point; however, the phrase "at least" is controverted by the term "about," which implies that values above and below the indicated amount are permitted. Therefore, the juxtaposition of these two terms makes it unclear what minimum purity is encompassed by the claim. In Amgen, Inc. v. Chugai Pharmaceutical co., 927 F.2d 1200 (CAFC 1991), the CAFC stated, "[t]he district court held claims 4 and 6 of the patent invalid because their specific activity of "at least about 160,000" was indefinite." After review, the CAFC states "[w]e therefore affirm the district court's determination on this issue." Thus, the CAFC found the phrase "at least about" indefinite where the metes and bounds of the term were not defined in the Specification.

3. Claim 22 is indefinite in the recitation "the LNA is 5'-biotin-TttTttTttTttTttTttTt." Claim 22 is dependent upon 18, wherein the LNA is complementary to a sequence consisting substantially of a poly(T) sequence (i.e., the LNA has a poly (A) sequence). It is unclear how 5'-biotin-TttTttTttTttTttTttTt is complementary to a sequence consisting substantially of a poly(T) sequence.

4. Claim 37 is indefinite in the recitation "the association constant (Ka) of the LNA oligonucleotide is higher" in lines 1-2 of the claim. It is unclear if the association

constant is for the LNA with itself or a complementary sequence. Claim 37 is also indefinite in the recitation (Ka) because it is unclear if (Ka) within the parenthesis is a limitation of the claim.

5. Claim 38 is indefinite in the following:

A. The recitation "the association constant (Ka) of the LNA oligonucleotide is higher" in lines 1-2 of the claim. It is unclear if the association constant is for the LNA with itself or a complementary sequence. There is also insufficient antecedent basis for this limitation of the claim. It is suggested that "the association constant" be changed to "a association constant."

B. The recitation "(Ka)" because it is unclear if (Ka) within the parenthesis is a limitation of the claim.

C. The recitation "the dissociation constant (Kd) of the complementary strand of the target sequence in a double stranded molecule" in lines 2-3 of the claim. It is unclear what the if the Kd refers to dissociation of the double stranded target or if Kd refers to dissociation of the target from a different double stranded molecule (e.g., a hybrid between the target and an antibody). There is also insufficient antecedent basis for this limitation of the claim. It is suggested that "the dissociation constant" be changed to "a dissociation constant."

D. The recitation "(Kd)" because it is unclear if (Kd) within the parenthesis is a limitation of the claim.

6. Claim 42 is indefinite in the recitation "the fluorescent signal" in lines 4-5 of the claim. There is insufficient antecedent basis for this limitation in the claim. It is suggested that the word "the" be changed to "a." Claim 42 is also indefinite in the recitation "the fluorescent signal from the nucleotide" at the end of the claim. There is insufficient antecedent basis for "the nucleotide" in the claim. It is also unclear how the nucleotide (i.e., a single base) creates a fluorescent signal.

7. Claims 43 and 113 are indefinite in the recitation "the Tm" in line one of each of the claims. There is insufficient antecedent basis for this limitation in the claim. It is suggested the word "the" e changed to "a."

8. Claim 58 is indefinite in the following:

A. The recitation "LNA containing a complementary overhang to a free arm in a dendrimer or a branched oligonucleotide" in lines 2-3 of the claim. It is unclear if "or" indicates that the branched oligonucleotide is a free arm contained in the complementary overhang or if the branched oligonucleotide is merely contained in the LNA.

B. The recitation "or biotin molecules" in lines 4-5 of the claim. It is unclear if the biotin molecules are an alternative to the complementary overhang or if the biotin molecules are an alternative to e.g., fluorescein isothiocyante.

C. The recitation "or fluorochrome molecules" in line 5 of the claim. It is unclear if the fluorochrome molecules are an alternative to the complementary overhang or if the fluorochrome molecules are an alternative to e.g., fluorescein isothiocyante.

D. The remaining recitations of the last 4 lines of the claim. The placement of the word "or" in lines 6 and 7 of the claim renders the claim unclear as to what the exact alternative embodiments are. It is suggested that the claim be amended to list the alternative embodiments similar to the format of claim 56.

9. Claim 59 is indefinite in the recitation "the sample" in the last line of the claim. There is insufficient antecedent basis for this limitation in the claim. It is suggested the claim be amended to reflect proper antecedent basis.

10. Claims 110-119 are indefinite in claim 110, which recites the limitation "the components" in line 7 of claim 110. There is insufficient antecedent basis for this limitation in the claim. It is suggested the claim be amended to reflect proper antecedent basis. Claims 110-119 are also indefinite in claim 110, which recites the limitation "the capturing probe" in line 10 of claim 110. There is insufficient antecedent basis for "the capturing probe" in "a capture probe." It is suggested "capturing" be changed to "capture."

11. Claim 117 is indefinite in the recitation "the retrovirus" in line 1 of the claim. There is insufficient antecedent basis for "the retrovirus" in "retroviruses" as found in claim 116. It is suggested the claim be amended to reflect proper antecedent basis.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5-11, 16, 18-21, 27, 29, 30, 33-43, 53-54, 74-76, and 91-92 are rejected under 35 U.S.C. 102(b) as being anticipated by Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999).

Regarding claim 1, Wengel et al teach a method for detecting an/or isolating a target nucleic acid molecule having a homopolymeric sequence comprising: treating a sample containing nucleic acid molecules with an LNA oligonucleotide to thereby detect and/or isolate a nucleic acid molecule having said homopolymeric sequence (e.g., poly dT primers containing LNA T residues are used to prime cDNA synthesis; page 181, Example 160).

Regarding claim 2, Wengel et al teach a method for detecting an/or isolating a target nucleic acid molecule having a repetitive element comprising: treating a sample

containing nucleic acid molecules with an LNA oligonucleotide to thereby detect and/or isolate a nucleic acid molecule having the repetitive element (e.g., poly dT primers containing LNA T residues are used to prime cDNA synthesis; page 181, Example 160).

Regarding claim 3, Wengel et al teach a method for detecting an/or isolating a target nucleic acid molecule having a conserved polynucleotide sequence comprising: treating a sample containing nucleic acid molecules with an LNA oligonucleotide to thereby detect and/or isolate a nucleic acid molecule having the conserved polynucleotide sequence (e.g., poly dT primers containing LNA T residues are used to prime cDNA synthesis; page 181, Example 160).

Regarding claim 5, Wengel et al teach the method of claim 1 wherein the LNA oligonucleotide is covalently attached to a solid support (e.g., LNA oligonucleotides are immobilized on a solid support; page 15, lines 7-9).

Regarding claim 6, Wengel et al teach the method of claim 1 wherein the LNA oligonucleotide is synthesized with an anthraquinone moiety and a linker at the at the 5'-end of the 3'-end of said oligonucleotide (e.g., the oligonucleotides carry an anthraquinone and a linker; page 62, lines 15-27).

Regarding claim 7, Wengel et al teach the method of claim 6 wherein the said linker is a higher hexaethylene glycol polymer (e.g., polyethylene glycol; page 21, lines 10-15).

Regarding claim 8, Wengel et al teach the method of claim 5 wherein said solid support is a polymer support is a polystyrene bead (page 62, lines 15-18).

Regarding claim 9, Wengel et al teach the method of claim 1, wherein the LNA oligonucleotide is complementary to a homopolymeric nucleotide comprising at least about one nucleobase that is different than the bases comprising the homopolymeric nucleic acid sequence (e.g., Probe RTZ5, 5'-**TTTTTTTTTT** [page 181, Example 160], wherein the LNA residues are in bold, and wherein the probe is complementary to a mRNA having a poly(A) tail [i.e., the poly (A) tail is the homopolymeric nucleotide] and the remainder of the mRNA has at least one nucleobase that is different from A; i.e., the message has the start codon AUG, which has bases other than A, which is the homopolymeric nucleic acid sequence).

Regarding claims 10-11, Wengel et al teach the method of claim 1 wherein the LNA oligonucleotide comprises at least about 10 repeating consecutive nucleotides (e.g., a poly dT LNA primer that is 15 bases long; page 181, lines 15-20).

Regarding claim 16, Wengel et al teach the method of claim 1 wherein the LNA oligonucleotide is complementary to a nucleotide sequence consisting substantially of a poly(A) nucleotide sequence (e.g., the LNA is a poly dT LNA; page 181, lines 15-20).
Regarding claim 6, Wengel et al teach the method of claim 1 wherein the LNA oligonucleotide is synthesized with an anthraquinone moiety and a linker at the at the 5'-end of the 3'-end of said oligonucleotide (e.g., the oligonucleotides carry an anthraquinone and a linker; page 62, lines 15-27).

Regarding claim 18, Wengel et al teach the method of claim 1 wherein the LNA oligonucleotide is complementary to a nucleotide sequence consisting substantially of a poly(T) nucleotide sequence (e.g., page 175, Example 154, wherein the LNA oligo 5'-d(**TGTGTGAAATTGTTA**) is complementary to dTTT, and wherein those bases in bold represent LNA nucleotides).

Regarding claim 19, Wengel et al teach the method of claim 1 wherein the LNA oligonucleotide is complementary to a nucleotide sequence consisting substantially of a poly(G) nucleotide sequence (e.g., page 163, Example 146, wherein the LNA oligo biotin-5'-d(**TTCCACAGCACA**A) is complementary to dGG).

Regarding claim 20, Wengel et al teach the method of claim 1 wherein the LNA oligonucleotide is complementary to a nucleotide sequence consisting substantially of a poly(U) nucleotide sequence (e.g., page 175, Example 154, wherein the LNA oligo 5'-d(**TGTGTGAAATTGTTA**) is complementary to rUUU).

Regarding claim 21, Wengel et al teach the method of claim 1 wherein the LNA oligonucleotide is complementary to a nucleotide sequence consisting substantially of a poly(C) nucleotide sequence (e.g., page 152, Example 137, wherein the LNA oligo 5'-d(GGTGG**TTTG**TTTG) is complementary to dCC).

Regarding claim 27, Wengel et al teach the method of claim 2 wherein the LAN oligonucleotide is complementary to a repetitive nucleotide sequence comprising at least one base that is different that the bases comprising the repetitive sequence (e.g.,

Seq. No 131, 5'-GTGTGGAT, which is complementary to 3'CACACACA except for the 2 base run of GA at the 3'end; page 169).

Regarding claim 29, Wengel et al teach the method of claim 1, wherein the LNA oligonucleotide is comprises at least one nucleotide having a nucleobase that is different from the nucleobases of the remaining oligonucleotide sequence (e.g., Probe No ATZ-1, 5'-Cy3-**TT**CC**A**C**A**C; wherein the A residues are different from the T and C residues of the rest of the sequence; page 171, line 23).

Regarding claim 30, Wengel et al teach the method of claim 1, wherein the -1 residue of the LNA oligonucleotide molecule 3' and/or 5' end is an LNA residue (e.g., Probe No ATZ-1, 5'-Cy3-**TT**CC**A**C**A**C; wherein the second T residue is an LNA; page 171, line 23).

Regarding claim 33, Wengel et al teach the method of claim 1, wherein the LNA oligonucleotide comprises at least about 20 to 50 percent LNA residues based on total residues of the LNA oligonucleotide (e.g., Probe No ATZ-1, 5'-Cy3-**TT**CC**A**C**A**C; wherein 4 of the 8 residues are LNA; page 171, line 23).

Regarding claim 34, Wengel et al teach the method of claim 1, wherein the LNA oligonucleotide comprises at least about 2 or more consecutive LNA molecules (e.g., Probe No ATZ-1, 5'-Cy3-**TT**CC**A**C**A**C; page 171, line 23).

Regarding claim 35, Wengel et al teach the method of claim 1, wherein the LNA oligonucleotide comprises modified and non-modified nucleotide molecules (e.g., Probe

No ATZ-1, 5'-Cy3-**TTCCACAC**; page 171, line 23, which has both LNA and non-LNA residues).

Regarding claim 36, Wengel et al teach the method of claim 1, wherein the LNA probe comprises a compound of the formula 5'-Y^q-$(X^p$-$Y^n)_m$-X^pZ-3' (e.g., Probe RTZ5, 5'-**TTTTTTTTTT**, where q=0, n=0, the first p = 6, the second p = 3, and Z is a dT residue at the 3' end; page 181, Example 160).

Regarding claim 37, Wengel et al teach the method of claim 1 wherein the association constant of the LNA oligonucleotide is higher that the association constant of the complementary strands of a double stranded molecule (e.g., LNA has a positive effect of the thermal stability of duplexes towards DNA and RNA; page 151, Example 135).

Regarding claim 38, Wengel et al teach the method of claim 1 wherein the association constant of the LNA oligonucleotide is higher that the dissociation constant of the complementary strand in a double stranded molecule (e.g., the LNA performs strand displacement on dsDNA; page 59, lines 23-29).

Regarding claim 39, Wengel et al teach the method of claim 1, wherein the LNA oligonucleotide is complementary to the sequence it is designed to detect and/or isolate (e.g., LNA-modified oligonucleotides function efficiently in the sequence specific capture of RNA molecules; page 182, lines 23-24).

Regarding claim 40, Wengel et al teach the method of claim 1, wherein the LNA oligonucleotide has at least one base pair difference to a complementary sequence it is

designed to detect and/or isolate (e.g., the LNA molecules detect end mismatches; page 170, example 152).

Regarding claim 41, Wengel et al teach the method of claim 40, wherein the LNA oligonucleotide can detect at least about one base pair difference between a complementary poly-repetitive sequence and the LNA/DNA oligonucleotide (e.g., the LNA molecules detect end mismatches [page 170, example 152], and the probes include poly repetitive sequences (e.g., Probe RTZ5, 5'-**TTTTTTTTT**T; page 181, Example 160).

Regarding claim 42, Wengel et al teach the method of claim 1, wherein the LNA oligonucleotide comprises a fluorophore moiety and a quencher moiety, positioned in such a way that a hybridized state of the oligonucleotide can be distinguished from an unbound state of the oligonucleotide by an increase in the fluorescent signal from the nucleotide (e.g., the LNA is a molecular beacon; page 64, lines 1-25).

Regarding claim 43, Wengel et al teach the method of claim 1, wherein the Tm of the LNA oligonucleotide is between about 50°C to about 70°C when the LNA oligonucleotide hybridizes to its complementary sequence (e.g., Tm No. 10, Table 1, page 184).

Regarding claim 53, Wengel et al teach the method of claim 1 wherein the LNA oligonucleotide is adapted for use an a molecular beacon (page 64, lines 1-25).

Regarding claim 54, Wengel et al teach the method of claim 1 wherein the LNA oligonucleotide hybridizes to complementary sequences of eukaryotic RNA (e.g., the

LNA are used to activate genes of therapeutic interest [page 60, lines 21-24], wherein the therapeutic applications are in humans; page 18, lines 5-6).

Regarding claim 74, Wengel et al teach the method of claim 1, wherein the LNA oligonucleotide comprises a fluorescent reporter molecule at one end of the molecule and a quencher molecule at a second end and wherein the reporter molecule is quenched by the quencher molecule with the LNA oligonucleotide is not hybridized to the nucleic acid molecules (e.g., the LNA is a molecular beacon, wherein the reporter [i.e., fluorophore] and quencher are at the ends of the molecule; page 64, lines 1-25).

Regarding claim 75, Wengel et al teach the method of claim 74, wherein hybridization of the LNA oligonucleotide is detected by detecting the increased fluorescence of the reporter molecules (page 64, lines 1-25).

Regarding claim 76, Wengel et al teach the method of claim 74, wherein the LNA oligonucleotide comprises, in addition to a sequence sufficiently complementary to said nucleic acid molecule to specifically hybridize to said nucleic acid molecule, a first and second complementary sequence which specifically hybridize to each other when the oligonucleotide is not hybridized to the nucleic acid molecule, bringing said quencher molecule in sufficient proximity to said reporter molecule to quench fluorescence of the reporter molecule (e.g., the molecular beacon forms a hairpin in the absence of the target; page 64, lines 1-10).

Regarding claim 91, Wengel et al teach the method of claim 54, wherein the LNA oligonucleotide hybridized to complementary sequences of mRNA (e.g., poly dT

probes [i.e., primers] containing LNA T residues are used to prime Arabidopsis mRNA; page 181, Example 160).

Regarding claim 92, Wengel et al teach a method for amplifying a target nucleic acid molecule the nucleotide sequence which is complementary to a LNA oligonucleotide capture probe, the method comprising: providing a sample containing nucleic acid molecules having repetitive base sequences (e.g., a sample with an sequence that binds to a first primer 5'-GGTGG**TTTG**TTTG-3', which contains the complement to the repetitive sequence GGTGGT; page 165, lines 10-15); and contacting the nucleic acid molecules from the sample with at least one LNA oligonucleotide capture probe to capture target nucleic acids (e.g., the LNA probe hybridizes to the targets; page 195, Example 148); and subjecting the captured nucleic acids to polymerase chain reaction, using primers to amplify the captured nucleic acid (e.g., the target is amplified in a PCR amplification using an additional primer in addition to the first primer [page 195, Example 148], and wherein captured nucleic acids are amplified directly on a surface; page 62, lines 4-10).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 1, 12-15, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) in view of Monforte et al (U.S. Patent No. 6,051,378, issued 18 April 2000).

Regarding claims 12-15, Wengel et al teach the method of claim 1 for detecting an/or isolating a target nucleic acid molecule having a homopolymeric sequence comprising: treating a sample containing nucleic acid molecules with an LNA oligonucleotide to thereby detect and/or isolate a nucleic acid molecule having said homopolymeric sequence (e.g., poly dT primers containing LNA T residues are used to prime cDNA synthesis; page 181, Example 160). While Wengel et al teach repeating nucleotides (e.g., poly dT primers containing LNA; page 181), Wengel et al do not teach oligonucleotides comprising at least about fifty nucleotides.

However, Monforte et al teach hybridization using capture probes that are 50 nucleotides in length with the added advantage that they provide stability to the hybridization of the capture probe (column 19, lines 40-42).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Wengel et al with the probe lengths as taught by Monforte with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because the modification would have provided stability to the hybridization of the capture probe as explicitly taught by Monforte et al (column 19, lines 40-42).

Regarding claim 17, the method of claim 15 is discussed above. Wengel et al also teach the LNA oligonucleotide is synthesized with an anthraquinone moiety and a linker at the 5'-end of said oligonucleotide (e.g., the oligonucleotides carry an anthraquinone and a linker; page 62, lines 15-27), wherein said linker is a higher hexaethylene glycol polymer (e.g., polyethylene glycol; page 21, lines 10-15). While Wengel et al teach LNA oligonucleotides covalently coupled to a solid polymer support (e.g., LNA oligonucleotides are immobilized on a solid support; page 15, lines 7-9) via excitation of the anthraquinone moiety using UV light (page 62, lines 23-26 and page 166, Example 149), Wengel et al do not specifically teach immobilization of the poly dT primers.

However, Wengel et al do teach that immobilization of nucleic acids is preferred because it allows hybridization and capture to occur simultaneously (page 62, lines 4-10).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method of claim 1 as taught by Wengel et al by immobilizing the LNA molecules as also taught by Wengel with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because the modification would have resulted in simultaneous hybridization and capture as explicitly taught by Wengel et al (page 62, lines 4-10).

3. Claims 1, 2, 4, 22, 25-26, 28, 44-52, and 127-135 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) in view of Skouv (U.S. Patent No. 6,303,315 B1, issued 16 October 2001).

Regarding claim 4, the method of claim 1 is discussed above. Wengel et al do not teach chaotropic agents.

However, Skouv et al teach the preparation of nucleic acids from biological samples using LNA and lysing in the presence of chaotropic agents (Abstract) with the added advantage that chaotropic agents facilitate lysis of the cells (column 1, lines 38-42).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified to method as taught by Wengel et al with the chaotropic agent as taught by Skouv with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in facilitation of the lysis of the cells as explicitly taught by Skouv (column 1, lines 38-42).

Regarding claim 22, the method of claim 1 is discussed above. Wengel et al also teach the LNA oligonucleotide is complementary to a nucleotide sequence consisting substantially of a poly(T) nucleotide sequence (e.g., page 175, Example 154, wherein the LNA oligo 5'-d(**TGTGTGAAATTGTTA**) is complementary to dTTT, and wherein those bases in bold represent LNA nucleotides). Wengel et al also teach oligo dT comprising (Table, page 183), as well as biotinylated LNA (page 19, lines 8-10), but do not specifically teach LNA at every third residue (i.e., compound 3 [SEQ ID NO. 3].

However, Skouv teaches an LNA oligomer having the formula (column 23)

$$G\text{-}[Nu\text{-}L]_{n(0)}\text{-}\{[LNA\text{-}L]_{m(q)}\text{-}[Nu\text{-}L]_{n(q)}\}_q\text{-}G^* \qquad V$$

wherein

q is 1–50;

each of n(0), . . . , n(q) is independently 0–10000;

each of m(1), . . . , m(q) is independently 1–10000;

with the proviso that the sum of n(0), . . . , n(q) and m(1), . . . , m(q) is 2–15000;

G designates a 5'-terminal group;

each Nu independently designates a nucleoside selected from naturally occurring nucleosides and nucleoside analogues;

each LNA independently designates a nucleoside analogue;

each L independently designates an internucleoside linkage between two groups selected from Nu and LNA, or L together with G* designates a 3'-terminal group; and

each LNA-L independently designates a nucleoside analogue of the general formula I as defined above.

which encompasses the alternating pattern of the instant claim, with the added advantage that the oligomers have good affinity and specificity in hybridization (column 24, lines 5-7).

It would therefore have been obvious to a person or ordinary skill in the art at the time the invention was claimed to have modified to method as taught by Wengel et al with the alternating LNA residues as taught by Skouv with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a

modification because said modification would have resulted in good affinity and specificity in hybridization as explicitly taught by Skouv et al (column 24, lines 5-7).

Regarding claim 25, the method of claim 18 and compound 3 [SEQ ID NO. 3] are discussed above. Wengel et al also teach the LNA oligonucleotide is synthesized with an anthraquinone moiety and a linker at the 5'-end of said oligonucleotide (e.g., the oligonucleotides carry an anthraquinone and a linker; page 62, lines 15-27), wherein said linker is a higher hexaethylene glycol polymer (e.g., polyethylene glycol; page 21, lines 10-15).

Regarding claim 26, the method of claim 18 and compound 3 [SEQ ID NO. 3] are discussed above. Skouv et al also teach LNA without biotin substitutions (e.g., the group G in the formula is a 5' terminal group).

Regarding claim 28, Wengel et al teach the method of claim 2 for detecting an/or isolating a target nucleic acid molecule having a conserved nucleotide sequence comprising: treating a sample containing nucleic acid molecules with an LNA oligonucleotide to thereby detect and/or isolate a nucleic acid molecule having the repetitive element (e.g., poly dT primers containing LNA T residues are used to prime cDNA synthesis; page 181, Example 160). Wengel et al do not teach one base different from the conserved sequence.

However, Skouv teaches the detection of at least one base different in a conserved region (e.g., missense mutations in conserved regions of highly conserved

regions of TP53) with the added advantage that missense mutations are indicative of tumors (column 2, lines 5-13).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method of Wengel et al with the at least one base differences as taught by Skouv with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in indicating the presence of tumors as explicitly taught by Skouv (column 2, lines 5-13).

Regarding claim 44, the method of claim 4 is discussed above. Skouv also teaches the chaotropic reagent is guanidinium thiocyanate (column 21, line 65-column 22, line 8).

Regarding claims 45-47, the method of claim 44 is discussed above. Skouv also teaches the concentration of guanidinium thiocyanate is at least about 4M (column 22, lines 1-8).

Regarding claim 48, the method of claim 44 is discussed above. Skouv also teaches hybridization at a temperature in the range of 20-65 °C (e.g., 37 °C; column 36, lines 40-50).

Regarding claim 49, the method of claim 48 is discussed above. The courts have stated where the claimed ranges "overlap or lie inside the ranged disclosed by the prior art" and even when the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have similar properties,

a *prima facie* case of obviousness exists (see *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990); *Titanium Metals Corp. of America v. Banner*, 778 F2d 775. 227 USPQ 773 (Fed. Cir. 1985) (see MPEP 2144.05.01). Therefore, the claimed ranges "at about 20 °C" is obvious over the 37 °C as taught by Skouv (column 36, lines 40-50).

Regarding claim 50, the method of claim 48 is discussed above. Skouv also teaches hybridization at a temperature of about 37 °C (column 36, lines 40-50).

Regarding claims 51 and 52, the method of claim 48 is discussed above. As stated above, when the claimed range is close enough that one skilled in the art would have expected them to have similar properties, a *prima facie* case of obviousness exists. Therefore, the claimed temperatures of about 55 °C and about 60 °C are obvious over the temperatures taught by Skouv (e.g., 37 °C [column 36, lines 40-50], and 70-100 °C; column 10, lines 53-56).

Regarding claim 127, the method of claim 1 is discussed above. While Wengel et al also teach high stringency hybridization at low salt concentration (e.g., selective binding occurs in low salt; page 183), Wengel et al do not teach chaotropic agents.

However, Skouv et al teach the isolation (i.e., preparation) of nucleic acids from biological samples using LNA and lysing in the presence of chaotropic agents (Abstract) with the added advantage that chaotropic agents facilitate lysis of the cells (column 1, lines 38-42).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified to method as taught by Wengel et al with the chaotropic agent as taught by Skouv with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in facilitation of the lysis of the cells as explicitly taught by Skouv (column 1, lines 38-42).

Regarding claims 128, the method of claim 127 is discussed above. Skouv also teaches the concentration of guanidinium thiocyanate is at least about 4M (column 22, lines 1-8).

Regarding claim 129, the method of claim 127 is discussed above. Skouv also teaches a binding buffer containing NaCl (column 4, lines 53-57).

Regarding claims 130-132, the method of claim 129 is discussed above. Skouv also teaches the NaCl concentration is less than 25 mM (e.g., between about 0 and 1M; column 4, lines 53-57).

Regarding claims 133-134, the method of claim 127 is discussed above. Skouv also teaches hybridization at a temperature of at least 37 °C (column 36, lines 40-50).

Regarding claim 135, the method of claim 127 is discussed above. Skouv also teaches hybridization at a temperature of at least 50 °C (e.g., 70-100 °C; column 10, lines 53-56).

4. Claims 1 and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) in view of Beier et al (Science, vol. 283, pp. 699-703 (1989).

Regarding claims 31 and 32, the method of claim 31 is discussed above. Wengel et al do not teach alpha-L LNA monomers or xylo-LNA monomers,

However, Beier et al teach locked nucleic acids comprising alpha-L LNA monomers and xylo monomers (e.g., Scheme 1) with the added advantage that the monomers are stronger Watson-Crick binders (Abstract).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified to method as taught by Wengel et al with the monomers as taught by Beier et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in stronger Watson-Crick binding as explicitly taught by Beier et al (Abstract).

5. Claims 1, 55, 56, 58, 59, 64-67, and 139 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999).

Regarding claim 55, the method of claim 1 is discussed above. Wengel et al also teach the LNA oligonucleotide is complementary to poly(A) tails in eukaryotic mRNA(e.g., poly dT probes [i.e., primers] containing LNA T residues are used to prime

Arabidopsis mRNA; page 181, Example 160) and where the said LNA oligonucleotide is synthesized with an anthraquinone moiety and a linker at the 5'-end of said oligonucleotide (e.g., the oligonucleotides carry an anthraquinone and a linker; page 62, lines 15-27), wherein said linker is a higher hexaethylene glycol polymer (e.g., polyethylene glycol; page 21, lines 10-15). While Wengel et al teach LNA oligonucleotides covalently coupled to a solid polymer support (e.g., LNA oligonucleotides are immobilized on a solid support; page 15, lines 7-9) via excitation of the anthraquinone moiety using UV light (page 62, lines 23-26 and page 166, Example 149), Wengel et al do not specifically teach immobilization of the poly dT primers.

However, Wengel et al do teach that immobilization of nucleic acids is preferred because it allows hybridization and capture to occur simultaneously (page 62, lines 4-10).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method of claim 1 as taught by Wengel et al by immobilizing the LNA molecules as also taught by Wengel with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because the modification would have resulted in simultaneous hybridization and capture as explicitly taught by Wengel et al (page 62, lines 4-10).

Regarding claim 56, the method of claim 55 is discussed above. Wengel et al also teach detection with probes using chemiluminescence (e.g., an LNA nucleoside has a

reporter group [page 9, lines 1-19], wherein the reporter group uses chemiluminescence; page 19, lines 8-20)

Regarding claim 58, the method of claim 56 is discussed above. Wengel et al also teach LNA probes having several digoxigenin molecules (e.g., an LNA nucleoside has a reporter group [page 9, lines 1-19], wherein the reporter group is digoxigenin [page 19, lines 8-10], wherein a probe has multiple LNA nucleosides [e.g., Probe RTZ5, 5'-**TTTTTTTTTT**, where each LNA nucleotide is in bold; page 181], and the reporter groups is detected by antibodies to it; page 19, lines 22-25).

Regarding claim 59, the method of claim 55 is discussed above. Wengel et al also teach contacting the sample with a polymerase and at least one nucleotide (e.g., mRNA is subjected to reverse transcription; page 181, Example 160).

Regarding claim 64, the method of claim 59 is discussed above. Wengel et al also teach the polymerase comprises a reverse transcriptase (e.g., the MRNA is subjected to a Reverse Transcriptase reaction; page 181, Example 160).

Regarding claim 65 and 67, the method of claim 59 is discussed above. Wengel et al also teach labeled LNA oligonucleotides (e.g., an LNA nucleoside has a reporter group [page 9, lines 1-19], and wherein a probe has multiple LNA nucleosides; e.g., Probe RTZ5, 5'-**TTTTTTTTTT**, where each LNA nucleotide is in bold; page 181).

Regarding claim 66, the method of claim 59 is discussed above. Wengel et al also teach the LNA oligonucleotide is bound to a solid support (e.g., the MRNA is subjected

to a Reverse Transcriptase reaction and an amplification reaction [page 181, Example 160], and said reactions occur directly on a surface; page 62, lines 8-10).

Regarding claim 139, the method of claim 56 is discussed above. Wengel et al also teach digoxigenin incorporated into nucleic acid probes (e.g., an LNA nucleoside has a reporter group [page 9, lines 1-19], wherein the reporter group is digoxigenin; page 19, lines 8-10)

6. Claim 57 is rejected under 35 U.S.C. 103(a) as being unpatentable over by Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) as applied to claims 55 and 56 above, and further in view of Bobrow et al (U.S. Patent No. 5,731,158, issued 24 March 1998).

Regarding claim 57, the methods of claim 55-56 are discussed above. While Wengel et al teach reporter groups (page 9, lines 1-19), Wengel et al does not teach tyramide signal amplification.

However, Bobrow et al teach tyramide signal amplification (column 4, lines 36-49) as a reporter system for nucleic acid binding systems (column 6, lines 49-55) with the added advantage that the reporter system allows quantitation of the presence of the analyte (Abstract).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method using reporter groups as taught by Wengel et al with the tyramide signal amplification reporter group as

taught by Bobrow et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because the modification would have resulted in allowing quantitation of the presence of the analyte as explicitly taught by Bobrow et al (Abstract).

7. Claims 60, 61, 69, 70, and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) as applied to claim 59 above, and further in view of Eberwine et al (U.S. Patent No. 5,514,545, issued 7 May 1996).

Regarding claim 60, the method of claim 59 is discussed above. Wengel et al are silent with respect to generating a plurality of copies of the eukaryotic mRNA.

However, Eberwine teaches a method of generating a plurality of copies of mRNA (e.g., amplification; column 4, lines 34-55) with the added advantage that amplification aids in the characterization of cell identity (Abstract).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Wengel et al with amplification as taught Eberwine et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because the modification would have resulted in aiding in the characterization of cell identity as explicitly taught by Eberwine (Abstract).

Regarding claim 61, the method of claim 60 is discussed above. Eberwine et al also teach a constant temperature (e.g., 4 hours at room temperature; Example 3).

Regarding claim 69, the method of claim 60 is discussed above. Wengel et al also teach the LNA oligonucleotide comprises a fluorophore moiety and a quencher moiety, positioned in such a way that a hybridized state of the oligonucleotide can be distinguished from an unbound state of the oligonucleotide by an increase in the fluorescent signal from the nucleotide (e.g., the LNA is a molecular beacon; page 64, lines 1-25).

Regarding claim 70, the method of claim 60 is discussed above. Wengel et al also teach detection of increased fluorescence of the molecular beacon (page 64, lines 1-25).

Regarding claim 73, the method of claim 59 is discussed above. Wenger et al do not teach adding a primer.

However, Eberwine et al tech a method of generating a plurality of copies of mRNA (e.g., amplification; column 4, lines 34-55) requiring primers (column 3, lines 1-10) with the added advantage that amplification aids in the characterization of cell identity (Abstract).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Wengel et al with amplification using primers as taught Eberwine et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the

modification because the modification would have resulted in aiding in the characterization of cell identity as explicitly taught by Eberwine (Abstract).

8. Claims 59-60, 62-63, 68, and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) as applied to claim 59 above, in further view of Gruenert et al (U.S. Patent No. 5,804,383, issued 8 September 1998).

Regarding claim 59, the method of claim 55 is discussed above. While Wengel et al also teach the method of claim 59 as discussed above, an alternate interpretation of contacting the sample with a polymerase and at least one nucleotide is taught by Gruenert et al, which teaches a method of generating a plurality of copies of mRNA (e.g., making and amplifying a cDNA copy of the mRNA using reverse transcriptase polymerase chain reaction; i.e., RT-PCR; Abstract) with the added advantage of allowing analysis of gene expression of specific alleles (Abstract).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Wengel et al to generate a plurality of copies of mRNA of as taught Gruenert et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because the modification would have resulted in allowing analysis of gene expression of specific alleles as explicitly taught by Gruenert et al (Abstract).

Regarding claim 60, method of claim 59 is discussed above. Gruenert et al also teach generating a plurality of copies of mRNA (e.g., making and amplifying a cDNA copy of the mRNA using reverse transcriptase polymerase chain reaction; i.e., RT-PCR; Abstract) with the added advantage of allowing analysis of gene expression of specific alleles (Abstract).

Regarding claim 62, the method of claim 60 is discussed above. Gruenert et al also teach cycling the temperature of the sample (e.g., conducting PCR on the sample; Abstract).

Regarding claim 63, the method of claim 60 is discussed above. Gruenert et al also teach a thermally stable polymerase (e.g., Taq (Is) DNA polymerase; column 25, lines 24-25).

Regarding claim 68, the method of claim 59 is discussed above. Wengel et al do not teach cells stably associated with a solid support.

However, Gruenert et al teach a method of generating a plurality of copies of mRNA (e.g., making and amplifying a cDNA copy of the mRNA using reverse transcriptase polymerase chain reaction; Abstract) comprising nucleic acid molecules in cells wherein the cells are stably associated with a solid support (e.g., the nucleic acids for the RT-PCR are in cells fixed to a slide then submitted to RT-PCR; column 8, lines 31-60) with the added advantage that the procedure destroys proteins and enzymes that interfere with PCR (column 8, lines 31-50).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Wengel et al to generate a plurality of copies of mRNA using cells stably associated with a solid support as taught Gruenert et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because the modification would have resulted in destruction of proteins and enzymes that interfere with PCR as explicitly taught by Gruenert et al (column 8, lines 31-50).

Regarding claim 72, the method of claim 59 is discussed above. Gruenert et al also teach rTh polymerase (column 9, lines 34-50).

9. Claim 71 is rejected under 35 U.S.C. 103(a) as being unpatentable over by Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) and Eberwine et al (U.S. Patent No. 5,514,545, issued 7 May 1996) as applied to claim 70 above, further in view of Eis et al (Nature Biotechnology, vol. 9, pp. 673-676, (July 2001))

Regarding claim 71, the method of claim 70 is discussed above. Neither Wengel et al nor Eberwine teach cleavage of the LNA (i.e., cleavage of the probe that captures the RNA).

However, Eis et al teach a method of capturing mRNA using invasive cleavage (Figure 1), wherein a probe is cleaved from the mRNA (Figure 1) with the added advantage that invasive cleavage allows direct quantitation of specific RNAs (Title).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Wengel et al with cleavage of the probe as taught Eis et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because the modification would have resulted in allowing direct quantitation of specific RNAs as explicitly taught by Eis et al (Title).

10. Claims 77-80 and 140 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) as applied to claims 59 above, in further view of Sambrook et al (*Molecular Cloning, A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, NY, pp. 5.58, 8.2, 8.3, 8.60-8.61, and 8.64-8.65 (1989)).

Regarding claim 77, the method of claim 59 is discussed above. Wengel et al do not teach adding a DNA polymerase.

However, Sambrook et al teach a method of amplifying mRNA comprising adding DNA polymerase, RNAse H (pages 8.60-8.61) and E. coli ligase after conversion of polyadenlylated mRNA to first strand complementary DNA under conditions suitable for generating double stranded complementary DNA (pages 8.64-8.65) with the added benefit of established a comprehensive cDNA library from a small quantity of mRNA (page 8.3, paragraph 1).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Wengel et al with amplification using the steps as taught Sambrook et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because the modification would have resulted in establishment of a comprehensive cDNA library from a small quantity of mRNA as explicitly taught by Sambrook et al (page 8.3, paragraph 1).

Regarding claim 78, the method of claim 77 is discussed above. Sambrook et al also teach insertion into a cloning vector (page 8.2).

Regarding claim 79, the method of claim 77 is discussed above. Sambrook et al also teach an anchor sequence for an RNA polymerase (e.g., a T7 RNA polymerase promoter; page 5.58, 5th paragraph).

Regarding claim 80, the method of claim 78 is discussed above. Sambrook et al also teach addition of T7 RNA polymerase to generate a plurality of RNA copies (page 5.58, first two paragraphs).

Regarding claim 140, the method of claim 79 is discussed above. Sambrook et al also teach T7 RNA polymerase (page 5.58, 5th paragraph).

11. Claims 1, 54, and 90 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) in view of Gottschling et al (U.S. Patent No. 5,916,752, issued 29 June 1999).

Regarding claim 90, the method of claim 1 is discussed above. Wengel et al also teach the method of claim 54 wherein the LNA oligonucleotide hybridizes to complementary sequences of eukaryotic RNA (e.g., the LNA are used to activate genes of therapeutic interest [page 60, lines 21-24], wherein the therapeutic applications are in humans; page 18, lines 5-6). Wengel et al do not teach yeast RNA.

However, Gottschling et al teach hybridization using yeast RNA with the added advantage that yeast RNA sequences have substantial sequence homology to the human RNA sequences (e.g., telomerase, column 17, line 64-column 18, line 5) and that yeast is a genetically tractable organism directly applicable to mammalian cells (column 23, lines 55-61).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Wengel et al with yeast RNA as taught by Gottschling et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because the modification would have resulted in RNA sequences with substantial homology to human sequences in an as explicitly genetically tractable organism directly applicable to mammalian cells as explicitly taught by Gottschling et al (column 17, line 64-column 18, line 5 and column 23, lines 55-61).

12. Claims 92 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) in view of Recker et al (U.S. Patent No. 5,691,153, issued 25 November 1997).

Regarding claim 93, Wengel et al teach the method of claim 92 for amplifying a target nucleic acid molecule the nucleotide sequence which is complementary to a LNA oligonucleotide capture probe, the method comprising: providing a sample containing nucleic acid molecules having repetitive base sequences (e.g., a sample with an sequence that binds to a first primer 5'-GGTGG**TTTG**TTTG-3', which contains the complement to the repetitive sequence GGTGGT; page 165, lines 10-15); and contacting the nucleic acid molecules from the sample with at least one LNA oligonucleotide capture probe to capture target nucleic acids (e.g., the LNA probe hybridizes to the targets; page 195, Example 148); and subjecting the captured nucleic acids to polymerase chain reaction, using primers to amplify the captured nucleic acid (e.g., the target is amplified in a PCR amplification using an additional primer in addition to the first primer [page 195, Example 148], and wherein captured nucleic acids are amplified directly on a surface; page 62, lines 4-10). Wengel et al are silent with respect to multiplex PCR.

However, Recker et al teach a method of screening nucleic acids (i.e., genome screening) using multiplex PCR with the added advantage that multiplex PCR increased the speed of throughput 10 fold (column 11, lines 20-32).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising PCR as taught by Wengel et al with multiplex PCR as taught by Recker al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because the modification would have resulted in increasing the speed of throughput 10 fold as explicitly taught by Recker et al (column 11, lines 20-32).

13. Claims 110-113 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) in view of Skouv et al (U.S. Patent No. 6,303,315 B1, issued 16 October 2001) and Alizon et al (U.S. Patent No. 5,310,651, issued 10 May 1994).

Regarding claim 110, Wengel et al teach a method for detecting an/or isolating a target nucleic acid molecule having a consecutively repeating base comprising: treating a sample containing nucleic acid molecules with an LNA oligonucleotide to thereby detect and/or isolate a nucleic acid molecule having said consecutively repeating base (e.g., poly dT primers containing LNA T residues are used to bind polyadenylated mRNA; page 181, Example 160). Wengel et al also teach LNA capture probes (e.g., LNA-modified oligonucleotides function efficiently in the sequence specific capture of RNA molecules; page 182, lines 23-24). Wengel et al do not teach chaotropic agents.

However, Skouv et al teach the preparation of nucleic acids from biological samples using LNA and lysing in the presence of chaotropic agents (Abstract)

concomitant with sample denaturation (column 47, lines 40-45) with the added advantage that chaotropic agents facilitate lysis of the cells (column 1, lines 38-42).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified to method as taught by Wengel et al with the chaotropic agent as taught by Skouv with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in facilitation of the lysis of the cells as explicitly taught by Skouv (column 1, lines 38-42). Neither Wengel et al nor Skouv teach RNA genomes form infectious diseases.

However, Alizon et al teach the isolation of genomic RNA from an infectious disease causing organism (e.g., isolation of RNA from HIV; column 11, lines 1-22) having consecutively repeating nucleic basis (e.g., Figure 1B) with the added advantage that genomic RNA allows for diagnosis (Abstract).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified to method as taught by Wengel et al and Skouv by using genomic RNA from an infectious disease organism as taught by Alizon et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing diagnosis as explicitly taught by Alizon et al (Abstract).

Regarding claims 111-112, the method of claim 110 is discussed above. Skouv also teaches guanidinium thiocyanate at a concentration of at least about 4M (column 22, lines 1-8).

Regarding claim 113, the method of claim 110 is discussed above. Skouv also teaches a Tm of about 70 °C (column 10, lines 53-56).

14. Claims 114-119 and are rejected under 35 U.S.C. 103(a) as being unpatentable over by Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) and Skouv et al (U.S. Patent No. 6,303,315 B1, issued 16 October 2001) and Alizon et al (U.S. Patent No. 5,310,651, issued 10 May 1994) as applied to claim 110 above, and as defined by Sambrook et al *Molecular Cloning, A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, NY, page 7.5 (1989)).

Regarding claims 114-115, the method of claim 110 is discussed above. Skouv also teaches guanidinium thiocyanate at a concentration of at least about 4M (column 22, lines 1-8). Skouv also teaches beta-mercaptoethanol in the lysing and hybridizing buffer (Abstract and column 4, lines 58-67). Sambrook et al define 4M guanidinium thiocyanate and beta-mercaptoethanol as RNAse inhibitors (page 7.5). It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that

subject matter shown to be in the prior art does not posses characteristic relied on" (205 USPQ 594, second column, first full paragraph). The inclusion of 4M guanidinium thiocyanate and beta-mercaptoethanol in the lysing buffer taught by Skouv is therefore and RNAse inhibitor as required by the claims.

Regarding claims 116-117, the method of claim 114 is discussed above. Alizon et al also teach the genomic RNA is isolated from the retrovirus HIV (Abstract).

Regarding claim 118, the method of claim 114 is discussed above. Alizon et al also teach the genomic RNA is used to genotype RNA viruses (e.g., the method detects HIV-2 [Abstract], a specific genotype of HIV).

Regarding claim 119, the method of claim 114 is discussed above. Alizon et al also teach the genomic RNA is used for diagnosis in a patient (e.g., the RNA is isolated from infected patients to indicate if HIV-2 is present; column 5, lines 19-28).

15. Claims 136-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) as applied to claim 56 above, and further in view of Squirrell et al (U.S. Patent No. 5,837,465, issued 17 November 1998).

Regarding claims 136-138, the method of claim 56 is discussed above. While Wengel et al also teach detection with probes using chemiluminescence (e.g., an LNA nucleoside has a reporter group [page 9, lines 1-19], wherein the reporter group uses

chemiluminescence; page 19, lines 8-20), Wengel does not specifically teach enzyme conjugated probes using chemiluminescence.

However, Baldwin et al teach nucleic acid probes with chemiluminescent enzymes (e.g. the bioluminescent enzyme luciferase; column 2, lines 14-26) with the added advantage that luciferase allows detection at very low concentrations using simple instruments (column 1, lines 15-20).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified to method as taught by Wengel et al by using luciferase as taught by Squirrell et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing detection at very low concentrations using simple instruments as explicitly taught by Squirrell et al (column 1, lines 15-20).

Conclusion

1. No claim is allowed.

2. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571) 272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Robert T. Crow
Examiner
Art Unit 1634

BJ FORMAN, PH.D.
PRIMARY EXAMINER